IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IDENIX PHARMACEUTICALS LLC UNIVERSITA DEGLI STUDI DI CAGLIARI, Plaintiffs, v. GILEAD SCIENCES, INC. Defendant.	C.A. No. 14-846-LPS

GILEAD'S LETTER
TO THE HONORABLE LEONARD P. STARK
IN RESPONSE TO PLAINTIFFS' NOTICE OF SUPPLEMENTAL AUTHORITY

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ATTORNEYS FOR DEFENDANT GILEAD SCIENCES, INC.

Dear Chief Judge Stark,

This letter responds to Idenix's notice regarding *UroPep v. Eli Lilly*. Idenix's notice ignores the nature of the invention at issue in *UroPep,* and contains numerous factual errors. After correcting Idenix's errors and misconceptions, the *UroPep* decision supports the invalidity of the '597 patent.

I. UroPep's Use Of A Well-Known Class Of Compounds With Known Activity Is Fundamentally Different Than The '597 Patent.

The state of the art at issue in *UroPep* could not be more different than that presented here. UroPep's patent claimed the use of selective PDE5 inhibitors to treat benign prostatic hyperplasia ("BPH"). *See UroPep* at 1. The "***mechanism of action***[1] [of PDE5 inhibitors] ***was well known*** before" the filing date. *Id.* at 23. "[***H]undreds*** of selective PDE5 inhibitors, as well as their function, ***were known*** in the art at the time of the invention." *Id.* at 18. Indeed, Lilly's expert acknowledged that "tadalafil [the accused product], as well as 118 other compounds disclosed in a document published in 1995, were known PDE5 inhibitors before the priority date of the '124 patent." *Id.* at 3. The field was so advanced that two PDE5 selective inhibitors were in human clinical trials at the time of filing. *Id.* at 15. And the specification itself identified four completely different known selective PDE5 inhibitors as working embodiments. *Id.* at 16. *UroPep* describes the patent as covering "***a group of compounds well known in the art***, including [the accused compound] . . ." *Id.* at 19. The process of synthesis of selective PDE5 inhibitors was so trivial "that at least tens of thousands have been developed since" the filing date of the patent. *Id.* at 16. This "mature" state of the art is very different than this case.

Drawing all reasonable inferences in Idenix's favor, as of the '597 filing date, the only sugar in the "class" of 2' methyl up compounds "active" against HCV that had ever been discovered was a single 2' methyl up, 2' OH down sugar design combined with one of four different bases. Idenix's expert testified that the field was in its "infancy in 2000-2001." Tr. 1927:23-1928:3 (Meier). Moreover, far from being "well known in the art," Idenix in its JMOL briefing claims that it was "miraculous" to find nucleosides active against HCV at the time of the patent and that "only a small number" of the vast combinations of 2' methyl compounds covered by the '597 patent structural limitations "could be active against HCV." D.I. 554 at 3-4. The inventor of the '597 patent acknowledged that the field was so immature that in 1999-2000, there were not "any modified ribonucleosides that were known to inhibit this replication for hepatitis C." Tr. 374:19-22. And while both the accused product and its mechanism of action were known as of the filing date in *UroPep*, neither was the case here. Idenix did not even include the concept of fluorine at the 2' down position in the '597 patent, and requested an inference that it was first able to make 2' methyl up, fluorine down in 2003 or 2005, after years of failed attempts. D.I. 565 at 6.

Idenix asserts that the Court must ignore these uncontroverted facts based on *UroPep*'s reference to "assume[ing] facts that the jury was not required to find." Dkt. 583, Ltr. at 2. Gilead does not ask the Court to "assume" anything. Rather Gilead asks the Court to fully credit the testimony of Idenix's witnesses, and "give credence . . . ***[to] that 'evidence supporting the moving party that is uncontradicted and unimpeached***'." *Integra v. Merck*, 496 F.3d 1334, 1345.

II. *UroPep*'s Discussion Of *Wyeth* Supports The Invalidity Of The '597 Patent.

[1] All emphasis is added unless otherwise noted.

UroPep observed that enablement does not turn merely on whether some amount of screening must occur. Instead, "[i]n the context of a disclosure and a field that provides no guidance, aimless plodding through systematic experimentation" "may be undue." *Id.* at 45. "[A]imless plodding through systematic experimentation" is exactly what the '597 patent asks a POSA to do. The '597 patent does nothing more than tell a POSA to engage in a trial and error process:

> "The βD-and β*L*-nucleosides of this invention ***may*** inhibit HCV polymerase activity. Nucleosides ***can be screened*** for their ability to inhibit HCV polymerase activity in vitro according to screening methods set forth more particularly herein. One can readily determine the spectrum of activity by evaluating the compound in the assays described herein or with another confirmatory assay." '597 patent (PX-1525), at 13:42-49; 36:43-59.
>
> "Compounds ***can*** exhibit anti-hepatitis C activity by inhibiting HCV polymerase, by inhibiting ***other enzymes*** needed in the replication cycle, or by ***other pathways***." *Id.* at 139:30-32.

Idenix cites to testimony from Dr. Meier that "the key of these compounds is the methyl group in the 2' position" and activity against the "HCV polymerase."[2] Tr. 1854:8-17, 1866:22-1868:11; 1918:11-19. But the only tool the experts point to for identifying activity against the polymerase is screening. Tr. 1855:1-1856:6 (Meier); Tr. 1969:24-1970:3 (DeFrancesco).

Idenix's suggestion that "common sense" could be used to dramatically decrease the scope of the research problem is not a ***reasonable*** inference from Dr. Secrist's testimony. Tr. 1723:5-20. In the cited passage, Dr. Secrist affirmed that under the Court's claim construction, at even one location (2' down) the number of options are "pretty much" "infinite." It was uncontradicted that within the specification the closed list of substituent options at that location numbered in the "thousands." Tr. 1597:5-1598:1. And the problem in the '597 patent claims is far worse -- there are open substituent positions at 1', 2' down, 3' up and down, 4' and 5'.

Idenix claims that "POSA's are used to working with large classes of compounds." Dkt. 583, Ltr. at 2. This case is not simply about a large class of candidate 2' methyl compounds; it is about the absence of any meaningful guidance beyond a recommendation to screen to find the "small" number of needles in the haystack. "[T]he specification provided 'only a starting point, a direction for further research.'" *Wyeth v. Abbott Labs.*, 720 F.3d 1380, 1386 (Fed. Cir. 2013) (citation omitted).

Idenix's reliance on Mr. Clark's creation of 2' methyl up, fluoro down to support enablement of the "full scope" of the claims turns the law of enablement on its head. First, Mr. Clark had to look beyond the '597 patent – Idenix's witness conceded that there is no disclosure of 2' fluoro down anywhere in the patent. D.I. 565 at 6. Second, the fact that Mr. Clark succeeded where Idenix repeatedly failed (by its own admission until 2003) does not show enablement as a matter of law. In *Liebel* "the inventors admitted that they tried unsuccessfully to produce a pressure-jacketless system and that producing such a system would have required more experimentation and testing." 481 F.3d 1371, 1379. The fact that the accused infringers were able to make a jacketless system was irrelevant to the Federal Circuit. The Federal Circuit in *Storer v. Clark* also declined to hold that Idenix enabled one of its patents based on Clark's work. 860 F.3d 1340, 1352 (Fed. Cir. 2017).

Idenix's reliance on a Pharmasset grant application's reference to "a class of 'potent' 2'-

[2] The specification actually says the opposite, identifying the polymerase as just one of many mechanisms through which the disclosed compounds might exhibit activity. PT-1525 at 139:30-32.

methyl ribonucleoside inhibitors," is a legal non-sequitur. PX0764.0023. That statement cites a 2001 patent application publication – not the '597 patent -- in which all of the claims were limited at each substituent location, and never included 2' fluoro down. The statement has no nexus to enablement of claims that were not pending at the time and did not issue until 2009. *C.f. W. Union Co. v. MoneyGram Payment Sys., Inc.,* 626 F.3d 1361, 1372-73 (Fed. Cir. 2010) (reversing denial of JMOL because patentee's evidence had no nexus to legal doctrine at issue).

Finally, the testimony Idenix touts that "tens of thousands of compounds can be routinely screened," misses the issue. First, Idenix ignores the uncontradicted testimony that POSAs could make only 2-3 nucleosides per month on average. Tr. 1562:19-1563:1. For Idenix, a company dedicated to nucleosides, synthesizing and then screening 37 molecules a month was "a lot." Tr. 1202:23-1203:6. In *Wyeth*, there was no assertion that synthesis was outside of the skill of a POSA, only that it was time consuming. 720 F.3d at 1386. Dr. Meier provided no testimony on the ***time*** it takes to synthesize. Second, the testimony Idenix relies on was identical to the testimony in *Wyeth,* in which a POSA "could routinely use the assays disclosed in the specification to determine" activity. *Id.* at 1385. As in *Wyeth*, because "the specification is silent on how to structurally modify [the 2' methyl up, 2' OH down sugar] to yield a compound having the recited functional effects" a trial and error process must occur that is the opposite of a patentable invention. *Id.* at 1384. Especially in a field in its "infancy in 2000-2001" where *"*you don't know whether or not a nucleotide will have activity against HCV until you make it and test it.*"* Tr. 1927:23-1928:3 (Meier), Tr. 1333:12-16 (Gosselin). As in *Wyeth*, the requirement for screening "confirmed the unpredictability of the art and the ensuing need to assay each candidate[.]" 720 F.3d at 1385.

Idenix caricatures the defects in the '597 patent by referencing *UroPep*'s observation that there is no requirement "for one artisan to synthesize ***all members of the genus***" "within a short period of time." *UroPep* at 42. But a specification "must enable a skilled artisan to practice ***the full scope*** of the invention" without undue experimentation. *Id.* In *UroPep*, a POSA could turn to the "hundreds" of known active selective PDE5 inhibitor compounds available as of the filing, including the very one accused of infringement. In fact, the field was so "mature" "that a skilled artisan would not necessarily need to conduct any screening but could 'use their own [PDE5 inhibitor] if they've got one already." *Id.* at 40. As a result, the time required to discover the 119th or 120th selective PDE5 inhibitor was simply not probative. In contrast, neither the state of the art nor the '597 patent itself directs a POSA to anything beyond the single sugar design that Idenix identifies as the "active" "working examples." In fact, this was Idenix's central theme at trial to defend against anticipation and obviousness: no POSA had ever discovered "any modified ribonucleosides that were known to inhibit this replication for hepatitis C." Tr. 374:19-22.

Thus, there is a vast difference between the state of knowledge in the UroPep patent at the time of filing and the '597 patent. Given this vast difference, it is unremarkable that what is required to be disclosed in the specification will be different. As *UroPep* explained:

> It is often the case that a patent claiming the invention of a new genus, or the use of a new genus, must provide more detail regarding that genus. . . . On the other hand, when a genus is well understood in the art and not itself the invention but is instead a component of the claim, background knowledge may provide the necessary support for the claim.

Id. at 19-20.[3] Idenix claims the use a "class" of ***all*** effective 2' methyl up compounds to treat HCV. Tr. 1860:3-6. But as of the priority date, only one design within that class had ever been discovered. As this Court has noted, "'[a] patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope of coverage.'" *Enzo I,* 2017 WL 2829625, at *3.

III. Idenix's "Four Factors" Confirm That The '597 Patent Is Invalid.

Idenix compares the UroPep patent to the '597 patent based on what it described as "four factors." This comparison affirms why the '597 patent is invalid under *Wyeth*.

Scope of the Claims. The UroPep claims require a very specific mechanism of action: the compound must be a selective inhibitor of PDE5. In contrast, the '597 patent claims are not limited to any specific mechanism of action. D.I. 536 at 8-9. All of Idenix's witness testimony and argument on JMOL arbitrarily assumes that the claims are limited to the HCV polymerase even though the specification teaches the exact opposite and the claims make no reference to the polymerase. PX-1525 at 139:30-32, 139:52-59. Moreover, Idenix ignores the fact that the required structure to perform the function of a PDE5 inhibitor was well known in the art. *UroPep* at 13 ("PDE5 inhibitors all share a common structural feature.").

The '597 patent claims are unlike the UroPep claims and instead are the mirror image of the Wyeth claims. Both the Idenix and Wyeth claims entail a broad structural limitation: 2' methyl up, any substituent but H at 2' and 3' down and any substituent at all at 1', 3' up, 4' and 5' for Idenix and "a macrocyclic triene ring structure produced by *Streptomyces hygroscopicus*" for Wyeth. 2012 WL 175023, at *3. Both then create a severe needle-in-a-haystack problem by limiting the genus to the "small" number of active members. As noted in *Wyeth*, "the number of compounds that would exhibit the recited functional effect would be significantly smaller." 720 F.3d at 1384.

Guidance in the Specification. Idenix states that "UroPep's patent also did not disclose a single selective inhibitor of PDE5 (much less any working examples of such compounds)." D.I. 583, Ltr. at 3. This representation is simply incorrect. "The specification of the '124 patent alone discloses at least four discrete compounds that were known to be selective PDE5 inhibitors, as well as two compound classes that were known to contain selective PDE5 inhibitors." *UroPep* at 16. *UroPep* found that "the specification provides working examples." *Id.* at 44. Idenix also wrongly states that UroPep's "claims excluded all preferred embodiments disclosed in the specification." D.I. 583, Ltr. at 3. As *UroPeP* explained, two of the selective PDE5 inhibitors listed in the specification – zaprinast and MY5445 – were not excluded by the claims. *UroPep* at 26. The process of synthesis of selective PDE5 inhibitors was so trivial "that at least tens of thousands have been developed since" the filing date of the patent. *Id.* at 16.

As to the '597 patent, Idenix points to a series of factors that emphasize the needle in a haystack problem created by the claims. In Formula XI of the patent, substitutions are allowed at the 1', 2' down, 3', 4' and 5' locations when 2' up is arbitrarily held to methyl. It was uncontroverted that at just one substituent location, there are "thousands" of options set out in the closed lists in the patent. Tr. 1597:5-1598:1. If changes are allowed at just three substituents locations, the combinations rapidly rise to 1 billion.

[3] The quoted portion of *UroPep* appears in the section addressing the written description challenge to UroPep's patent. But it applies with equal force to the enablement issue. *See, e.g.*, *UroPep* at 39-40.

Idenix points to "working examples," "Fig 1" and "synthetic routes." But all of these involve a single sugar design, with 2' methyl up, 2' OH down and the identical substituents at all other locations. Tr. 1849:10-1850:2 (Meier); 1863:11-15; 1922:18-1925:3. This is not a "contested fact[]" as Idenix suggests; it is the testimony of Idenix's own expert, Dr. Meier.

Development of the Field. *UroPep* held that the field of the patent was "a mature field in which skilled artisans knew what PDE5 inhibitors were and had already discovered hundreds of them. Those representative species would indicate to a skilled artisan at the time of the invention that selective PDE5 inhibitors such as tadalafil, well known in the mature field in 1997, would work in the claimed invention." *UroPep* at 16-17.

The field of the '597 patent is very different. Dr. Meier testified that the "field" of "modified nucleosides for HCV" was in its "infancy in 2000-2001." Tr. 1927:23-1928:3. Idenix claims that "the field of modifying nucleosides for use as viral treatments was well known and routine." D.I. 583, Ltr. at 3. But the claims of the '597 patent do not just require the synthesis of any nucleoside, nor activity against any virus. The claims require activity against the HCV virus, a field in which Idenix's brief argues it was "miraculous" to find an active molecule.[4] D.I. 554 at 3.

Extent of Screening. Idenix suggests that the extent of screening required by the UroPep patent was much greater than the '597 patent. Not so. *UroPep* concluded that "a skilled artisan ***would not necessarily need to conduct any screening***" to practice the full scope of the invention. *Id.* at 40. This is because a POSA could simply access the extraordinary number of PDE5 selective inhibitors that were known in the art before the priority date and rapidly created after the filing date. "[H]undreds of selective inhibitors of PDE5 were known at" the time of filing (*id.* at 3) and "at least tens of thousands have been developed since" the filing date of the patent (*id.* at 16). In contrast, if there were a tool in the '597 patent specification other than screening to identify active 2' methyl compounds, both Drs. Meier and DeFrancesco were unable to point to it.

IV. The Written Description Dispute In *UroPep* Is Different From The '597 Patent

Idenix quotes *UroPep*'s observation that "the possession inquiry is not limited to what is expressly described within the 'four corners' of the specification" but instead is "an objective one that is viewed from the perspective of a person of ordinary skill in the art." *UroPep* at 12. The opinion addressed an issue different than the written description defects in the '597 patent. The UroPep patent expressly recited that its invention was the use of all selective PDE5 inhibits to treat BPH. D.I. 583, Ex. B at 2:18-20. Lilly was simply challenging whether enough examples were included in the specification. The opinion noted that it was proper for a POSA to consider the "hundreds" that were available at the time of the patent. In contrast, there is no statement in the '597 patent that the invention is any 2' methyl up active nucleoside, with ***anything*** but H at 2' down. This is because all substituent lists in the specification are ***closed***, and never include fluorine at 2' down. And separately it is because the only molecule design ever identified as active is the single sugar with 2' methyl up, 2' OH down and the same substituents at all other locations. There are no "hundreds" of active 2' methyl nucleosides known in the art for a POSA to consider when reading the patent.

[4] Only one 2' methyl nucleoside has ever made it through FDA approval.

Respectfully submitted,

/s/Joseph B. Warden

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JBW:pfc

cc: All Counsel of Record – via e-filing